

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 47,642
FECHA : JULIO 1 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-007930- -00004-0000

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Act. 400 OPOSIOBSERVTER Folios: 55

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	114281053	18/06/2009	4,305,000.00
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	114645996	27/03/2009	1,722,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LEAS COMERCIALES	287,000.00
		TOTAL :	\$ 287,000.00

SON: DOSCIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

PODER ESPECIAL

Yo, **LUIS PALACIOS ARAGÓN**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **GYNOPHARM S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHÓRQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 08 7930, titulada "**COMPOSICIONES FARMACEUTICAS DE LIBERACION SOSTENIDA Y PROCESOS DE LAS MISMAS**", cuyo titular es **PANACEA BIOTEC LIMITED**, publicada en la gaceta No. 602 del 31 de marzo de 2009.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los ____ días del mes de ____ de 2009.

GYNOPHARM S.A.

Cédula de Extranjería: No. 319788.

NIT: 802.096.279-4

Representante Legal

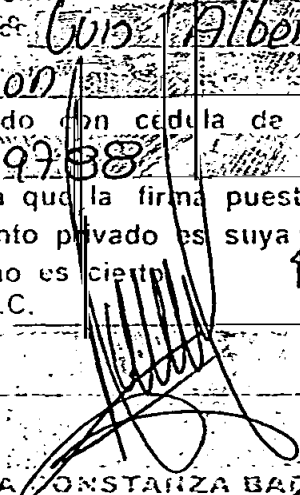
Acepto:

ELIANA ISAURA MORENO BOHÓRQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

RECONOCIMIENTO DE DOCUMENTO PRIVADO

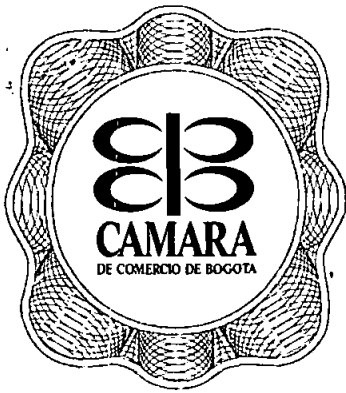
Ante mí, LILIANA CONSTANZA BARBOSA PLATA,
 Notaria Veintitrés del Circuito de Bogotá (E).
 comparece Guis Alberto Palacios
Aragon
 identificado con cédula de ciudadanía
CC 319788
 y declara que la firma puesta en el presente
 instrumento privado es suya y que el contenido
 del mismo es cierto. **16 JUN. 2009**
 Bogotá D.C.
 FIRMA: 


 LILIANA CONSTANZA BARBOSA PLATA
 NOTARIA VEINTITRÉS

NOTARIA PRIMERA DE CHIA
PRESENTACION PERSONAL

Este memorial dirigido a Sopei Intendencia de Industria y comercio
 fué presentado personalmente ante el suscrito notario por Elieno Iscua
Morano Bohorquez.
 Identificado C.C. 51975664 Bogotá
 T.P. de Abogado No. 83823
 Chia 01 JUL 2009





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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/06/19

HORA: 13:11:00

OPERACION: 10ERP0619107

PAGINA: 1

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 3,551 del 17 de Dic/bre de 1997, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 18 de Dic/bre de 1997 bajo el No. 72,965 del libro respectivo, fue constituida la sociedad-----
anonima denominada GYNOPHARM S.A. -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/c documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
532	1999/03/25	Notaria 3a. de Barranquilla	80,373	1999/04/13

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

GYNOPHARM S.A.-----

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 802.006.279-4.

MATRICULA MERCANTIL: 245,470.

C E R T I F I C A

Direccion para notificaciones judiciales:

CR 49 C No 80 - 125 OF 512.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 16 de Dic/bre de 2047.

C E R T I F I C A

OBJETO SOCIAL: a) La fabricacion de capsulas y otro productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/06/19

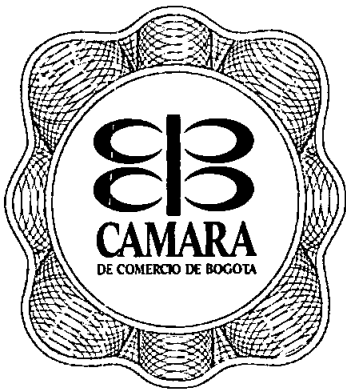
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uso y consumo humano y veterinario. b) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal. c) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos, medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. e) Actuar como representante o agente de personas naturales y juridicas nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualesquiera de las actividades descritas en los literales a), b), c) y d) antes transcritos. f) Prestar los servicios de asesoria y consultoria en las areas administrativa, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de GYNOPHARM S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial. g) Adquirir, operar, administrar y explotar, a cualquier titulo, empresas o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto; comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

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general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o lo de sus socios.-----

C E R T I F I C A

CAPITAL

Nro Acciones

Valor Acción

Autorizado

\$*****4,000,000,000 *****4,000,000 *****1,000

Suscrito

\$*****2,672,646,000 *****2,672,646 *****1,000

Pagado

\$*****2,672,646,000 *****2,672,646 *****1,000

C E R T I F I C A

ADMINISTRACION: Seran funciones de la junta directiva, entre otras:
Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion y para enajenar o gravar bienes inmuebles y demas activos fijos de la sociedad, cualquiera que sea la cuantia de la transaccion. Las demas que le sean propias y no esten atribuidas a otro organo social y las que le correspondan en virtud de la ley. la sociedad tendra un Gerente General, quien ejercera la administracion y representacion legal de la sociedad y tendra las siguientes atribuciones, entre otras: Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto. Para enajenar, a cualquier titulo, bienes inmuebles de la sociedad o constituir gravámenes sobre los mismos, debera obtener la aprobacion de la junta directiva, cualquiera que sea la cuantia de la transaccion; o las demas funciones que le corres-

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SE BARRANQUILLA S.A. N.T. N.E. C.I. 1111 10884 01 2004

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

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pondan como representante legal por disposicion de la ley, de estos estatutos o de la junta directiva. El Gerente General tendra un suplente, designado por la junta directiva, quien lo reemplazara con identicas facultades en sus faltas temporales, absolutas o meramente accidentales, sin que sea necesario para ello acreditar la ausencia del principal.-----

C E R T I F I C A

Que según Acta No. 15 del 18 de Febrero de 2008 correspondiente a la Asamblea de Accionistas en Bogota, de la sociedad:

GYNOPHARM S.A.-----

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 25 de Febrero de 2008 bajo el No. 137,919 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

- | | |
|---|--------------------|
| 1. Llobet Poal Manuel | CC.*****14,670,196 |
| 2. Zanatta Reheman Leonardo Andres | CC.*****2,760,271 |
| 3. Munoz Marroquin Diego | CC.*****7,688,292 |
| 4. Montealegre Gonzalez Andres Leonardo | CC.*****79,950,262 |

Suplentes

- | | |
|-----------------------------------|--------------------|
| 1. Agudelo Pelaez Luis Hernando | CC.*****14,238,997 |
| 2. Aroca Almanza Arleth Ayelina | CC.*****36,718,415 |
| 3. Penaranda Urbina Adriana Paola | CC.*****53,120,683 |
| 4. tovar Vasquez Ruth | CC.*****52,175,756 |

C E R T I F I C A

Que según Acta No. 18 del 30 de Octubre de 2003 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Nov/bre de 2003 bajo el No. 107,783 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General. /	
Palacios Aragon Luis Alberto	CE.*****319,788

C E R T I F I C A

Que según Acta No. 49 del 03 de Marzo de 2008 correspondiente a la

*** CONTINUA ***



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

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Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 11 de Marzo de 2008 bajo el No. 138,342 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Mollajoli Centurion Andres Fernando	CE.*****351,283

C E R T I F I C A

Que según Acta No. 19 del 30 de Abril de 2009 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 27 de Mayo de 2009 bajo el No. 149,314 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal.	
PENALOSA AUDITORES & ASOCIADOS S.A.	Ni.*****830,095,635

C E R T I F I C A

Que por Documento Privado del 11 de Mayo de 2009, otorgado en Bogota por Peñalosa Auditores & Asociados S.A. inscrito en esta Cámara de Comercio, el 27 de Mayo de 2009 bajo el Nro 149,315 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Designado: Revisor Fiscal Ppal	
Padilla Romero Ivan Dario	CC.*****80,025,798
Designado: Revisor Fiscal Suplente	
Gomez Preciado Clara Judith	CC.*****52,544,226

C E R T I F I C A

Que según Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 23 de Noviembre del 2.000 bajo el No. 1.872 del libro repectivo, consta que el señor RUBEN MINSKI GONTOVNIK C.C. No. 7.463.982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficiente a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.-732.070, para que en nombre y representacion de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

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S.A., en el giro normal de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 12 de junio del 2.002, bajo el 2.164 del libro respectivo, consta que el señor JORGE CASTELLANOS MARTINEZ, identificado con C.C.No.19.460.089, actuando como representante legal de la sociedad GYNOPHARM S.A, otorga Poder Especial Amplio y Suficiente a KAREN FIGUEROA GARCIA, identificada con la cedula de ciudadania No.32.732.070 de Barranquilla, mediante documento privado de octubre 10/2000, inscrito en la Camara de Comercio de Barranquilla bajo el No.1.872 del libro respectivo, para que en representacion de GYNOFARM S.A, suscriba las declaraciones cambiarias a los que esta obligada GYNOFARM S.A. en el giro ordinario de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

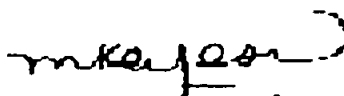
C E R T I F I C A

Que su última Renovación fue el: 31 de Marzo de 2009.

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en Certificados Especiales.

C E R T I F I C A

Que los actos de registro aquí certificados quedan en firme cinco días hábiles despues de la correspondiente inscripción, siempre que, dentro de dicho término, no sean objeto de los recursos de reposición ante esta entidad, y/o de apelación para ante la Superintendencia de Industria y Comercio.



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 December 2002 (27.12.2002)

PCT

(10) International Publication Number
WO 02/102415 A1

- (51) International Patent Classification⁷: **A61K 47/38**, 9/52, 9/22
- (21) International Application Number: PCT/IN02/00096
- (22) International Filing Date: 2 April 2002 (02.04.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
559/MUM/2001 18 June 2001 (18.06.2001) IN
- (71) Applicant (for all designated States except US): **BLUE CROSS LABORATORIES LIMITED** [IN/IN]; A-12, Ambad Industrial Area, Nashik 422 010, Maharashtra (IN).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **AVACHAT, Makarand, K.** [IN/IN]; 9 Sanjay Apartments, Racca Colony, Nashik 422 002, Maharashtra (IN). **DHAMNE, Abhijit, G.** [IN/IN]; 12 Jaigopal Society, Near Jawahar Market, Nashik Road 422 101, Maharashtra (IN).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report
— with amended claims and statement
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 02/102415 A1

(54) Title: GASTRIC FLOATING SYSTEM

(57) Abstract: A solid controlled release oral, buoyant unit dose pharmaceutical composition, which comprises of one or more therapeutic agent/drug, a gel forming husk powder obtained from *Lepidium Sativum* seeds, one or more cross-linking enhancer, one or more gas generating component and pharmaceutically acceptable excipients. The gel forming husk powder obtained from *Lepidium sativum* seeds is present in amounts of between 5 to 60 % of the total weight of dosage form, the cross-linking enhancer is selected from xanthan gum, karaya gum and the like in amounts of from 0.5 to 10 % by weight of the dosage form, gas generating component in amounts of from about 5 % to 20 % by weight of the composition to give a release profile of between 4 to 12 hours. The total excipients added is between 10 to 40 % by weight of the total dosage form. The composition may be in the form of a tablet capsules and pellets. The therapeutic agent/drug used in the composition is selected from drugs that are absorbed predominantly from the upper parts of gastrointestinal tract.

GASTRIC FLOATING SYSTEM

Field of invention

The present invention relates to a gastro-retentive oral drug delivery system
5 comprising at least one drug substance, a gel forming husk separated from
Lepidium sativum seeds, cross-linking enhancer, gas generating component, and
pharmaceutically acceptable auxiliary components. The pharmaceutical
composition is in the form of a single layer or bilayer tablets, capsules or pellets
retained in the stomach by swelling and floating mechanism and thereby
10 selectively delivering the desired drug in gastric medium and upper part of the
small intestine over an extended period of time.

Background of invention

15 Because of advancement in controlled release technology, it is now possible to
release drugs at a constant rate for long periods of time ranging from days to
years. But these benefits of long-term delivery technology cannot be completely
extrapolated for dosage forms intended for oral administration. This is mainly due
to complex anatomy and physiology of gastrointestinal tract. Due to this, an orally
20 administered drug delivery system is exposed to a wide range of highly variable
conditions such as pH, agitation, intensity, short gastric emptying times
composition of gastrointestinal fluids during its transit through the digestive tract.

The critical adversities in development of controlled release dosage form are short
25 gastric residence time and unpredictable gastric emptying time. The relatively
brief gastrointestinal transit time is the most difficult hurdle in development of
once a day dosage form, especially for those molecules with short absorption
window. The average transit time from mouth to colon is the time available for

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drug absorption regardless of the duration of the drug release from the device. Therefore, for drugs having prominent absorption from stomach or upper parts of small intestine conventional approaches to controlled release formulation known in the art are not useful. Furthermore, it is advantageous to retain the dosage form in stomach to have local activity of drugs like anti-ulcer, drugs acting against H. pylori infections etc. A sustained release formulations, which slowly releases the drug over an extended period and at the same time retained in upper parts of gastrointestinal tract for a prolonged period would be desirable for diseases confined to the upper parts of gastrointestinal tract such as peptic and duodenal ulcers.

In the prior art various approaches have been pursued to increase the retention of an oral dosage form in stomach. Broadly these can be classified as follows :

- 15 (I) Floating systems also known as hydrodynamically balanced systems (HBS)
 - i) Non-effervescent
 - ii) Effervescent
- (II) Swelling and expanding systems
- 20 (III) Bioadhesive systems
- (IV) Modified shape systems
- (V) High density systems
- (VI) Delayed gastric emptying devices

(I) Floating systems

1. Floating systems also known as Hydrodynamically balanced system (HBS). Based on the mechanism of buoyancy, two distinctly different technologies are defined.

- 5 a. Non-effervescent
- b. Effervescent

a. Non Effervescent floating drug delivery systems :

In non-effervescent FDDS floating is achieved due to inherent physical properties like Molecular weight, rate of hydration and swelling behavior of polymers. These polymers are gel-forming or highly swellable, cellulose type hydrocolloids polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene. In these floating systems, desired buoyancy is achieved due to entrapment of air in swollen gel structure after
15 penetration of gastrointestinal fluid.

Gerogiannis et al described floating swelling characteristics of various polymers used for controlling the release of active medicament. He concluded that the higher molecular weight of polymer and slower rates of polymer hydration are
20 usually necessary for enhanced floating behavior of system (DDIP, 19(9), 1993, 1061-108321)

U.S. patent no. 4,126,672, 4,167,558 described buoyant floating tablets and capsules containing one or mixture of hydrocolloids that hydrate and swell upon
25 contact with gastric fluid and acquire bulk density of less than one.

U.S. patent no. 5,232,704 described bilayer, sustained release dosage form. One layer was drug release layer and other was a buoyant or floating layer. Each layer contained hydrocolloid gelling agent such as gums, polysaccharides, Hydroxypropyl methyl cellulose. Patent claimed, buoyancy of system in gastric fluid for a period upto about 13 hrs.

U.S. patent no. 4,814,179 described non-compressed sustained release floating therapeutic composition containing agar and light mineral oil. The light mineral oil used helps in preventing entrapped air from escaping when system is placed in gastric fluid and thus system attend buoyancy.

Watanbe et al used empty globular shells with a lower density than gastrointestinal fluid. They used polymers such as polystyrene, cellulose acetate phthalate, ethyl cellulose and Hydroxypropyl methyl cellulose. But there was problem of incorporation of drugs into such system.

b. Effervescent floating drug delivery systems :

These buoyant delivery systems utilize matrices prepared with swellable polymers such as Hydroxypropyl methyl cellulose, Hydroxypropyl cellulose or polysaccharides for eg. Gums, chitosan and effervescent part for eg. Sodium bicarbonate, Calcium carbonate etc and citric acid / tartaric acid or matrices containing liquid portion that gasify at body temperature.

The gas generating component(s) may be intimately mixed within the tablet matrix to produce single layered tablet or a bilayered tablet which contains one gas generating component and other release controlling ingredient mixed with

Ichikawa et al described a new multiple unit oral floating system consisting of sustained release pills as seeds and double layers of gas generating components coated on seeds. Author claimed excellent floating ability independent of pH and viscosity of medium and has sustained release characteristics of zero order, but those who are skilled in the art are well aware of the limitations of such system for incorporating high dosage of drugs. (JPS, 80(11), 1991, 1062-1066).

Atyabi and co-workers developed floating system utilizing ion exchange resins.

The system consisted of resin beads loaded with bicarbonate and then coated with semi-permeable membrane. Drug especially carrying negative charges was bound to the resin. In acidic environment Carbon dioxide generated and trapped in membrane and beads were carried towards the top of gastric contents producing a floating layer of resin beads. (JOCR, 42, 1996, 25-28).

Patent no. WO 00/15198 (PCT) and WO 01/64183 described a very complicated floating drug delivery system comprising of a drug, a gas generating component, a swelling agent, a viscolyzing agent and a gel forming polymer. This system used higher percentage of superdisintegrant class of polymers as swelling agent combination with viscolyzing agent / gel forming polymer entrapping gas, generated due to gas generated component. According to claims, system retained in upper part of gastrointestinal tract releasing drug in controlled rate. The system is complicated due to presence of so many controlling and floating ingredients. It is not cost effective in terms of manufacturing as well as packing is concerned, as it will require special packing to protect it from moisture.

crosslinked gelatin, crosslinked albumin, crosslinked sodium alginate, crosslinked carboxymethyl cellulose, crosslinked PVA and crosslinked chitin.

U.S. patent no. 5,58,2837 described a system with plurality of particles of drug
5 mixed with alkyl cellulose such as Hydroxyethyl cellulose or Hydroxypropyl cellulose which swell after imbibition of water to enhance gastric retention in stomach.

U.S. patent no. 6,306,439 described expandable pharmaceutical forms for long
10 gastric residence employing mixtures of polymers containing lactum groups and polymers containing carboxyl group, gas generating component. Inventors claimed polymer swelling and high dimensional stability swollen state.

[III] Bioadhesive systems are used to localize a delivery device within stomach
15 cavity using bioadhesive polymers.

[IV] Modified shape systems are non-disintegrating geometric shapes molded
from silastic elastomers or polyethylene blends. Depending upon size and
shape, gastric residence time can be extended.

20

[V] High density formulation having density greater than 1 (g/cm^3), can be used
to increase gastric residence time. This can be achieved by coating the drug
with heavy inert material such as barium sulphate, zinc oxide, titanium
dioxide etc.

25

From the above discussed prior art it is crystal clear that increased gastric

biocompatible, overcome all drawbacks of existing systems, devoid of the use of any synthetic polymers, easy to manufacture on the industrial scale. The components used therein should be user-friendly.

5 In the present invention a novel gel-forming husk powder separated from seeds of *Lepidium sativum* is used. This husk prepared by the process of the invention possess mucilaginous property because of which it swells in the presence of biological fluid forming hydrogel like structure in combination with cross linking enhancer. The gas generated due to gas forming component gets entrapped in this
10 porous but stiff matrix resulting in increase in buoyancy of system and thus system floats in gastric environment. This structure formed due to swelling and entrapment of gas is sufficiently cohesive. This dual mechanism ensures that the system remains floated for long time without losing integrity and continues to release the drug at a desired rate.

15

In our co-pending Indian patent application No. 560/MUM/2001 there is described and claimed a method of manufacturing of husk from *Lepidium sativum* husk from *Lepidium sativum* seeds.

20 *Lepidium sativum* mainly consists of polysaccharides, which comes under the class of compounds called as 'dietary fiber'. For the purpose of definition in this specifications the term, "dietary fiber" is defined as remnants of plant cells resistant to hydrolysis by alimentary enzyme of man, the group of substances that remain in ileum but are partly hydrolysed by bacteria in colon according to JAMA
25 262, No. 4, 542546 (Jul 28, 1989) Gel forming dietary fibers include mucilages, plant gums, pectins or pectin substances and lignin, all of which are endogenous

stomach or intestine. Chemically nearly all of these plant materials are carbohydrates composed of repeating sugar (monosaccharides) units. Water-soluble fraction of these substance form gels in stomach and intestinal tract. Gums and mucilage have different structure but are polysaccharides, containing several

5 sugars with alternating monomer structures and may or may not contain uronic acids. There are many mucilage and gum containing seeds found in plants and cereal grains. Guar and locust bean gums are galactomannans, whereas gum Arabic is an acidic polymer of galactose and rhamnose. Oat and barley contain

10 gums, but are not practical for use in present application due to low percentage of active gum or weight volume. In present application 'Cress seed Husk' is principle gel forming dietary fiber. This cress seed husk is obtained from seeds of Garden Cress Plant (*Lepidium Sativum*, Family : *Cruciferae*) cultivated as a salad plant throughout India. Garden Cress is a small, herbaceous, glabrous, annual

15 growing plant up to 50 cm. From ancient times, Garden Cress seeds, leaves, roots and flowers are regularly used for treating various diseases or disorders. Seeds are mainly used as laxative, aperients, diuretic, and alternative tonic, demulcent, aphrodisiac and carminative. Mucilage of seeds allays the irritation of mucous coat of intestine.

20 Analysis of Cress seed gave following compositions. Moisture 5.69 %, protein 23.5 %, fats 15.91 %, ash 5.7 %, phosphorous (P_2O_3) 1.65 %, Calcium 0.31 % and sulfur 0.9 %. The seeds contain an alkaloid (0.19 %) Glucotropoelin sinapin (Choline ester of sinapic acid), Sinapic acid, Mucilaginous matter (5 %) and uric acid (0.103 %). The mucilage consists of a mixture of cellulose (18.3 %) and

25 uronic acid containing polysaccharides, acid hydrolysis of mucilage yields L-arabinose, D-galactose, L-rhamnose, D-galactouronic acid and D-glucose.

27

The seed of garden cress is old household remedy for various disorders or diseases. Seeds are recommended for the dispersion of certain chronic enlargement of spleen. Emulsion made by soaking or boiling the seeds in eight times the weight of water, is given as a drink to relieve hiccups. (Bhavprakash, an ancient
5 standaed book on Ayurveda) a powder of seed with sugar is fien remedy for indigestion, diarrhoea and dysentery. Seeds in combination with Coconut, ghee, sugar is very nutritious and is given to pregnant women and lactating mothers in the form of Laddoos. Thus there are quite a few references in ancient standard Indian medicinal books regarding safe consumption of seed of *Lepidium sativum*.

10

A toxicity study was made on *Lepidium sativum* seeds using Wistar albino rats at 2 % (w/w) was found to be non-toxic, 10 % (w/w) was toxic but not fatal and 50 % (w/w) of the diet for 6 weeks was lethal and caused depression in growth rate and entero-hepato-nephrotoxicity

15

Patole et al studied the antidiabetic activity of *Lepidium sativum* seeds on 11 NIDDM subjects as well as 14 normal healthy subjects by administering 15 gm. seeds per day. In the long term (21 days) treatment they found that seeds possess some hypoglycemic activity.

20

Thus there is no toxicity observed at therapeutic as well as formulation level. All above information proves that Garden Cress seeds are very safe material with respect to human consumption beyond doubt.

25 None of the publications report sustained release formulations being application of a porous matrix formed by the use of a natural biocompatible gelling and

swelling agent to give buoyancy and sustained release. Furthermore, polymers used in all above cases are mostly synthetic in origin.

OBJECTS OF THE INVENTION

5

Thus it is an object of the present invention to provide a pharmaceutical composition in the form of capsule, tablet single layered or multi-layered, pellets, which constitutes a gastro-retentive controlled oral drug delivery system that:

- 10 a. Swell / expand to form a porous, cohesive structure in which gas formed due to reaction between gas generating component and acid present in stomach, get entrapped, reducing density of system.
- b. remain buoyant for substantial period of time, delivering the drug in a controlled manner, in stomach.
- 15 c. maintain its shape and integrity for substantial period of time.
- d. provides, as compared to other oral controlled drug delivery systems, increased absorption of drug having a narrower absorption window.

It is also an object of the present invention to use a novel viscosity imparting inert
20 food item which is very cost effective viz. *Lepidium sativum* husk.

It is further object of this invention to use the floating system effectively and efficiently for acidic, basic as well as neutral drugs.

25 It is further object of this invention to use the floating system effectively and efficiently for low as well as high dose medicament.

SUMMARY OF THE INVENTION

The present invention described a system for oral administration in the form of tablet, capsule, bilayer tablets, pellets which is buoyant in stomach, extending
5 gastric residence time. The delivery system is structurally composed of a porous, cohesive matrix with large volume of entrapped air making it light and imparts good floatation characteristics.

The present invention describes a therapeutic system in the form of capsule,
10 tablet, single layered or multi-layered, pellets, essentially comprises of drug, hydrogel forming husk powder separated from *Lepidium sativum* seeds, cross-linking enhancer(s), gas generating component/(s) and other pharmaceutically acceptable auxiliary components.

15 Preferably, the oral controlled drug delivery system of the present invention, which is in the form of tablets single layered or multi-layered, capsule or pellets, comprises of an amount ranging from a pharmaceutically acceptable amount up to 90 % of drug, about 2 to about 60 % by weight of hydrogel forming husk from *Lepidium sativum* seeds, 0.5 to 20 % cross-linking enhancer(s), about 5 to 20 %
20 by weight of gas generating component(s) and pharmaceutically acceptable auxiliary components.

Detailed description of the invention

25 According to the present invention, the oral pharmaceutical composition in the form of capsule, tablet, single layered or multi-layered, pellets includes, at least one drug substance, gel forming husk powder separated from *Lepidium sativum*

seeds, cross-linking enhancer(s), a gas generating agent(s) and pharmaceutical auxiliary component(s).

According to present invention matrix forming components are natural, safe, bio-compatible and bio-degradable dietary fiber in presence of crosslinking enhancer
5 which form porous but cohesive hydrogel which entraps gas generated due to gas generating component(s) in presence of gastric fluid, releasing drug in a controlled manner over a period of time

10 The task of designing a dosage form to achieve a consistent and controlled residence in the stomach begins with selection of potential excipients, especially polymers used for forming porous but cohesive structured gel which can withstand bursting effect imparted by gas generating components, but at the same time allow the drug to diffuse slowly enough to serve as a 'reservoir' for delivery
15 system.

Lepidium sativum husk mainly consists of polysaccharides, especially cellulose and uronic acid. In the presence of gastric fluid, cellulose micelles swell and form a network, interspersed with more heavily hydrated polyuronide chains forming a
20 cohesive gel like structure.

Among the various parameters that need to be evaluated for their effect on gastric residence time 'dissolution' is the main parameter. For floating dosage form, there must be some modifications of USP / BP dissolution apparatus (type I or II), as
25 these apparatus inhibit the three dimensional swelling process of the dosage form and consequently drug release from the formulation was suppressed. Also these

overcome these problems and to adopt realistic and simulative approach to in vivo condition, Pillay and Fassihi et al approach was adopted of submerged ring / mesh assembly. This approach gave acid test to dosage form giving full surface exposure and unhindered swelling.

5 (JOCR, 55,(1998), 45-55).

The composition in present invention may be in the form of tablets, capsules bilayer or multilayer floating tablet or pellets. Additional polymers known to those who are skilled in the art are used for their release retarding property in
10 combination with *Lepidium sativum* husk as cross-linking enhancer. These polymers may be hydrophilic or hydrophobic in nature or may be pH dependent or independent polymers. Examples of suitable polymers are cellulose ethers like methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, eudragit, ethyl cellulose, gum, pectins, alginates and its derivatives, polyvinyl
15 alcohol, gelatin, cellulose derivatives etc. To improve gastro-retentive properties bioadhesive polymers can also be incorporated. Also some highly swelling polymers may also be added to increase the size of the dosage form to improve gastric retention.

20 The described composition of present invention when added to simulated gastric fluids can float on the fluid for about 10-12 hours or more. Due to presence of acid and gas generating component(s), gas is liberated and gets entrapped in swelled / gelled matrix, due to which there is decrease in specific gravity of system and system produces upward motion and remain there due to buoyancy.

25 Generally density of gastric fluid is 1.0 g/cm^3 and desired density of system should be around 0.7 g/cm^3 . The drug incorporated within this porous matrix is

released over a period of time while system is retained in gastric and upper part of the small intestine, due to floating and swelling.

The various components of present invention are described below:

5

A]. Lepidium sativum Husk

Lepidium sativum husk in combination with cross-linking enhancer(s) when formulated in the form of tablet, single layered or multi-layered, capsule, pellets produces a hydrogel matrix. This is a three dimensional, water-swollen structure
10 composed of mainly hydrophilic homopolymers or copolymers. They are rendered insoluble due to the presence of chemical or physical cross-links. The physical cross-links can be entanglements, crystallites or weak van der Waals forces or Hydrogen bonds. The cross-links provide the network structure and physical integrity.

15

Cress seed husk in presence of biological fluid in gastrointestinal tract absorb water and swell. This swelling property of husk is mainly because of mucilaginous matter present in it. The mucilage consists of a mixture of cellulose (18.3 %) and uronic acid containing polysaccharides. This in presence of water,
20 the polyuronide chains, containing ionisable carboxyl groups, become hydrated and swell and the cellulose micelles become dispersed. Thus gel consists of a network of hydrated cellulose micelles, interspersed with more heavily hydrated uronide chains. The extent of dispersion depends upon ultimately on the size of the cellulose micelle, the chain length and the proportion of hydrated
25 polyuronides. Because of their high water content and rubbery nature, they

giving a porous and cohesive matrix. Thus system is biocompatible, biodegradable and devoid of any unwanted characteristic side effects of synthetic polymers, which are traditionally used to modify drug release. Because of natural source of *Lepidium sativum* husk, presence in abundance, easy cultivation and
5 amount required to extend the delivery of therapeutic agent is optimum; use of this dietary fiber is very cost effective.

In swelling controlled release systems, the drug is dispersed within a glassy polymer. Upon oral ingestion and contact with gastric fluid, the controlled release
10 formulations prepared according to the present invention begin to swell and gel. Gas generated due to gas generating component(s) get entrapped in this swollen matrix results in increased buoyancy of the system. This buoyant system then floats in biological fluid releasing the drug in a controlled manner. Since the medicament is dispersed throughout the tablet (and consequently throughout the
15 gel matrix), a constant amount of drug can be released per unit time in vivo by dispersion or erosion of the outer portions of the matrix. The chemistry of *Lepidium sativum* husk, which is the essential part of the present invention, is such that it is considered to be self-buffering agents, substantially insensitive to the solubility of the medicament and likewise insensitive to the pH changes along
20 the length of the gastrointestinal tract.

In a preferred embodiment of present invention the pharmaceutical composition comprised from about 5 to 80 % by weight of husk separated from *Lepidium sativum* seeds. In a preferred embodiment, pharmaceutical compositions
25 comprised from about 5 to 60 % by weight of husk separated from *Lepidium sativum* seeds.

B| Cross-linking enhancer(s)

Cross-linking enhancer(s) mainly helped in binding individually swollen or swelling husk particles by forming a chain and thus controlling the pore or
5 channel size. It also plays a role in increasing the viscosity of system internally so that there was proper engulfment of drug or therapeutic agent particles inside the matrix releasing them in a controlled manner.

Gums, such as, gellan gum, carragennan gum, karaya gum, tragacanth gum, ghatti
10 gum, glucomannan, guar gum, gum acacia, locust bean gum, xanthan gum, veegum, gellan gum and cellulose derivatives like hydroxy propyl methyl cellulose, hydroxy propyl cellulose, carboxymethyl cellulose and its derivatives, pectins, lignin, chitins and its derivatives, acrylic acids and its derivatives, agar, gelatin, polyvinyl alcohol and carbopols or a combination of more than one
15 thereof, can be used as cross-linking enhancer(s).

In a preferred embodiment of present invention the cross-linking enhancer(s) comprised from about 0.5 to 25 % by weight of total weight of composition. In a more preferred embodiment, cross-linking enhancer(s) comprised from about 0.5
20 to 20 % by weight of total weight of composition.

C| Gas generating component(s)

The gas-generator may consist of a single substance known to produce Carbon
25 dioxide or Sulfur dioxide upon contact with gastric fluid. Examples of gas generators that may be used in the present invention include Carbon dioxide

such as sodium hydrogen carbonate or potassium hydrogen carbonate, Sulfur dioxide generators such as sodium sulfite, sodium bisulfite or sodium metabisulfite and the like.

- 5 The gas-generator interacts by simply with gastric fluid to generate carbon dioxide or sulfur dioxide that gets entrapped within the hydrated gel matrix of the swelling composition. The gas-generators such as carbonates and bicarbonates may be present in amount from about 5 % to 20%, preferably from about 5% to 15%, by weight of the composition.

10

D) Drug

- According to the present invention, the pharmaceutical composition is in the form of tablets single layered or multi-layered, capsule or pellets as a unit oral gastro-
15 retentive controlled release dosage form. The drug(s), which can be incorporated in the present system, may be therapeutically active or may be converted into the active form by biotransformation in the body.

- The medicament or combination of medicaments which are amenable to
20 controlled release therapy utilizing the novel formulations of the present invention include any those suitable for oral administration. The present invention is not to be construed as being limited to any particular medicament or class of medicaments.

- 25 The gastro-retentive formulations of the subject invention are particularly amenable to the administration of medicaments which have following attributes,

- i) drugs having pH dependent solubility, i.e., more soluble in the gastric pH as compared to the intestinal pH,
- ii) are predominantly absorbed through the upper portion of the gastro intestinal tract,
- 5 iii) drugs active against *H. pylori*, cytoprotective agents, and the like.
- iv) drugs having stomach as a site of action, which includes H-2 receptor antagonists, antacids, antimuscarinic agent, proton pump inhibitors

Illustrative examples of drugs that are absorbed predominantly from the upper
10 parts of gastrointestinal tract include ofloxacin, metoprolol, oxprenolol, baclofen, allopurinol ciprofloxacin, cyclosporin, furosemide, , sumatriptan, benazepril, enalapril, quinapril, imidapril, benazeprilat, cilazapril, captopril, delapril moexipril, indolapril, olindapril, retinapril, pentopril, perindopril, altiopril, quinaprilat, ramipril, spirapril, cilazeprilat, lisinopril, , tosinopril, libenzapril,
15 spiraprilat, zofenopril and the like; of which are suitable for use in the present invention.

This invention can be used for drugs active against *H. Pylori* like bismuth salts such as bismuth ranitidine bismuth citrate, subsalicylate, tripotassium
20 dicitratobismuthate, and the like; The H-2 receptor antagonists such as cimetidine, ranitidine, famotidine, nifentidine, roxatidine, nizatidine, bifentidine, erbrotidine and the like; and the like; antacids like aluminium hydroxide, magnesium oxide, magnesium carbonate, and the like; cytoprotectives such as carbenoxolone sodium sucralphate, and the like; antimuscarinic agents like propanthelene
25 bromide, pirenzepine, telenzepine and the like; antibiotics for example amoxycillin, clarithromycin and the like; all of which are suitable for use in the

Drugs having solubilities in acidic pH or one with absorption site in upper part of the gastro-intestinal tract and those that are subjected to gastro-intestinal first pass metabolism. These are antihypertensive agent like diltiazem hydrochloride, 5 nimodipine, nicardipine, amlodipine, verapamil, nefedipine, propranolol, prazosin, ketanserin, guanabenz acetate, hydralazine, carvedilol, methyldopa, levodopa, carbidopa; antivirals like pranobex, zidovudine (AZT), acyclovir, inosine, tribavirin, vidarabine; lipid lowering agents like atorvastatin, pravastatin, simvastatin, and lovastatin; antipsychotic agents like selegiline; sedatives like 10 midazolam; all of which are suitable for use in the present invention.

The drug itself or its pharmacologically active salt or ester can be used in the present invention. Moreover, combination of drugs that are typically administered together may be included as the drug component. The amount of drug is that 15 which is typically administered for a given period of time. Accordingly, the drug may be present in amount ranging from a pharmaceutically acceptable amount up to 90% by weight of the total weight of the composition.

E) Pharmaceutical Auxiliary components

20

According to the present invention the pharmaceutical composition may contain one or more of water soluble or insoluble diluent. Preferably the water soluble and or insoluble diluents were present in an amount from about 1 to 40 % weight of total weight of composition.

25

Examples of water-soluble diluents that were used in present invention include

insoluble diluents that were used in present invention include but not limited to Dibasic Calcium Phosphate, Starch and Microcrystalline cellulose.

Pharmaceutically acceptable binder(s) such as Polyvinylpyrrolidone 30/90,
5 Hydroxypropyl methylcellulose, and hydroxypropylcellulose can be used in present formulation in an amount ranging from 0.2 % to 10.0 % by weight either alone or in combination. In addition to the above ingredients, pharmaceutical grade anti-adherent and Colloidal silicon dioxide (Aerosil 200) as a lubricant are included in matrix formulation. Preferably magnesium stearate or stearic acid, talc
10 and colloidal silicon dioxide are present in an amount ranging from 0.2 % to 5.0 % by weight either alone or in combination. Other pharmaceutical auxiliary components, which may be used by one skilled in the art to formulate the therapeutic system. Antioxidants can also be added. The choice of auxiliary components and the amounts to be used is considered to be within the purview of
15 one skilled in the art.

The tablets may be film-coated with rapidly dissolving water-soluble film forming polymer like hydroxypropyl methylcellulose, acrylate, ethyl cellulose or with water-soluble excipients and many more. The tablet may be coated to weight
20 build up of about 1 to 4 % by weight preferably from about 1 % to 2 % by weight

Preferably the coating composition contains colouring agent and an opacifier in order to improve appearance.

DETAILED DESCRIPTION OF PROCEDURE OF MAKING UNIT

DOSAGE FORM

Here detailed procedure for making tablet dosage form is described. According to
5 process for making the composition of present invention the biologically
absorbable drug or therapeutic agent, gel forming husk separated from *Lepidium
sativum seeds*, a cross-linking enhancer(s), gas generating component(s) and
water soluble and or insoluble diluents were first sifted through 250µm sieve and
then mixed together in octagonal blender. In non-aqueous vehicle preferably
10 Isopropyl alcohol, binder polyvinylpyrrolidone or Hydroxypropyl
methylcellulose, or hydroxypropyl cellulose was dissolved under stirring.
Isopropyl Alcohol without Polyvinylpyrrolidone can also be used. Granulation
was carried out in planetary mixer or Rapid Mixer Granulator. Granules were
dried in Fluidized Bed Dryer. Dried granules were sifted through 1 mm sieve
15 (BSS 16#) to reduce particle size. Then blend was lubricated using the above
mentioned lubricant and then after mixing in octagonal blender was compressed
into tablets.

The tablets may be coated with rapidly dissolving water-soluble film forming
20 polymer. The tablet may be coated to weight build up of about 1 to 4 % by weight
preferably from about 1 % to 2 % by weight.

Preferably the coating composition contains colouring agent and an opacifier in
order to improve appearance.

Example 1:

Ofloxacin is representing molecule with moderate dose and moderate solubility. Tablets were made by compression at usual press (4 to 10 kg/cm²) according to following formula.

Ingredients	mg/tab	Percentage
Ofloxacin	400.0	48.48
Garden Cress husk	230.0	27.87
Xanthan gum	23.0	2.78
Lactose	40.0	4.85
Sodiumbicarbonate	100.0	12.12
Polyvinylpyrrolidone 90	5.0	0.61
Magnesium stearate	6.0	0.72
Talc	8.0	0.97
Aerosil-200	8.0	0.61

Ofloxacin, Garden Cress Husk, Xanthan gum, Lactose, Sodium bicarbonate were sifted through 250µm (BSS 40 #) sieve and mixed well. Polyvinylpyrrolidone 90 was dissolved in Isopropyl Alcohol and granulated the above blend in planetary mixer. Granules were dried in Fluidized Bed Dryer (FBD) at 50°C and passed through 1 mm (BSS 16#). Dried and sifted granules were lubricated with Aerosil 200, Magnesium Stearate and Talc and compressed the blend for preparing tablets.

Dissolution was performed as per USP XXIV in 1.0 liter, 0.1 N Hydrochloric acid, 100 RPM, at 37°C using apparatus 1. Release profile was as follows:

TIME (HOUR)	% DRUG DISSOLVED
1	45.82
3	61.81
5	69.13
8	80.45
10	86.22

Example 2:

Ingredients	mg/tab	Percentage
Ofloxacin	400.00	49.08
Garden Cress husk	250.00	30.67
Xanthan gum	25.00	3.07
Starch	50.00	6.13
Sodiumbicarbonate	60.00	7.36
Polyvinylpyrrolidone 90	12.00	1.47
Magnesium stearate	10.00	1.00
Talc	5.00	0.61
Aerosil-200	3.00	0.37

5

Ofloxacin, Garden Cress Husk, Xanthan gum, Starch, Sodium bicarbonate were sifted through 250 μ m (BSS 40 #) sieve and mixed well. Polyvinylpyrrolidone 90 was dissolved in Isopropyl Alcohol and granulated the above blend in planetary mixer. Granules were dried in Fluidized Bed Dryer (FBD) at 50°C and passed
10 through 1 mm (BSS 16#). Dried and sifted granules were lubricated with Aerosil 200, Magnesium Stearate and Talc and compressed the blend for preparing tablets.

Dissolution was performed as per USP XXIV in 1.0 liter, 0.1 N Hydrochloric
15 acid, 100 RPM, at 37°C using modified basket. Release profile was as follows:

TIME (HOUR)	% DRUG DISSOLVED
1	27.91
2	37.86
4	57.51
6	70.61
8	79.02
12	89.52

Example 3: Trial with hydroxypropyl methylcellulose as cross-linking enhancer

Ingredients	mg/tab	Percentage
Ofloxacin	400.00	47.39
Garden Cress husk	250.00	29.62
Methocel K-100M CR	25.00	2.96
Lactose	50.00	5.92
Sodiumbicarbonate	90.00	10.66
Polyvinylpyrrolidone 90	8.00	0.95
Magnesium stearate	10.00	1.18
Talc	6.00	0.72
Aerosil-200	5.00	0.59

5

Ofloxacin, Garden Cress Husk, Methocel K-100M CR, Lactose, Sodium bicarbonate were sifted through 250 μ m (BSS 40 #) sieve and mixed well.

Polyvinylpyrrolidone 90 was dissolved in Isopropyl Alcohol and granulated the above blend in planetary mixer. Granules were dried in Fluidized Bed Dryer (FBD) at 50°C and passed through 1 mm (BSS 16#). Dried and sifted granules were lubricated with Aerosil 200, Magnesium Stearate and Talc and compressed the blend for preparing tablets.

Dissolution was performed as per USP XXIV in 1.0 liter, 0.1 N Hydrochloric acid, 100 RPM, at 37°C using apparatus 1. Release profile was as follows:

15

TIME (HOUR)	% DRUG DISSOLVED
1	52.63
2	60.65
4	74.16
6	85.30
8	92.38

Example 4:

Diltiazem Hydrochloride is representing an acidic molecule with moderate dose
 5 and high water solubility. Tablets were made by compression at usual press (4 to
 8 kg/cm²) according to following formula.

Ingredients	mg/tab	Percentage
Diltiazem Hydrochloride	120.0	33.33
Garden Cress husk	150.0	41.67
Xanthan gum	30.0	8.33
Sodiumbicarbonate	25.0	6.94
Dibasic Calcium Phosphate	15.0	4.17
Polyvinylpyrrolidone 90	10.0	2.78
Magnesium stearate	4.0	1.11
Talc	3.0	0.83
Aerosil-200	3.0	0.83

Diltiazem Hydrochloride, Garden Cress Husk, Xanthan gum, Dibasic Calcium
 0 Phosphate and Sodium bicarbonate were sifted through 250µm (BSS 40 #) sieve
 and mixed well. Polyvinylpyrrolidone 90 was dissolved in Isopropyl Alcohol and
 granulated the above blend in planetary mixer. Granules were dried in Fluidized
 Bed Dryer (FBD) at 50°C and passed through 1 mm (BSS 16#). Dried and sifted
 granules were lubricated with Aerosil 200, Magnesium Stearate and Talc and
 5 compressed the blend for preparing tablets.

Dissolution was performed as per USP XXIV in 1.0 liter, 0.1 N Hydrochloric

TIME (HOUR)	% DRUG DISSOLVED
1	23.49
2	33.17
4	44.34
8	53.97
12	64.57

Example 5:

Ciprofloxacin is representing a molecule with high dose and low water solubility.

- 5 Ciprofloxacin tablets were made by compression at usual press (4 to 10 kg/cm²) according to following formula.

Ingredients	mg/tab	Percentage
Ciprofloxacin USP	1000.0	81.96
Garden Cress husk	100.0	8.2
Xanthan gum	10.0	0.82
Sodiumbicarbonate	80.0	6.55
Polyvinylpyrrolidone 90	5.0	0.4
Magnesium stearate	7.0	0.57
Talc	10.0	0.82
Aerosil-200	8.0	0.65

- Ciprofloxacin USP, Garden Cress Husk, Xanthan gum and Sodium bicarbonate
10 through were sifted 250µm (BSS 40 #) sieve and mixed well.

- Polyvinylpyrrolidone 90 was dissolved in Isopropyl Alcohol and granulated the
above blend in planetary mixer. Granules were dried in Fluidized Bed Dryer
(FBD) at 50°C and passed granules through 1 mm (BSS 16 #). Granules were
15 lubricated with Aerosil 200, Magnesium Stearate and Talc and compressed the
blend for preparing tablets.

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Dissolution was performed as per USP XXIV in 1.0 liter, 0.1 N Hydrochloric acid, 100 RPM, at 37°C using apparatus 1. Release profile was as follows:

TIME (HOUR)	% DRUG DISSOLVED
1	53.57
2	66.12
4	82.89
5	86.89

5 Example 6:

Acyclovir is representing molecule with moderate dose and high solubility. Tablets were made by compression at usual press (4 to 10 kg/cm²) according to following formula.

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Ingredients	Mg/tab	Percentage
Acyclovir	400.00	49.08
Garden Cress husk	250.00	30.67
Xanthan gum	25.00	3.07
Starch	50.00	6.13
Sodiumbicarbonate	60.00	7.36
Polyvinylpyrrolidone 90	12.00	1.47
Magnesium stearate	10.00	1.23
Talc	5.00	0.61
Aerosil-200	3.00	0.37

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Acyclovir, Garden Cress Husk, Xanthan gum, Starch, Sodium bicarbonate were sifted through 250µm (BSS 40 #) sieve and mixed well. Polyvinylpyrrolidone 90 was dissolved in Isopropyl Alcohol and granulated the above blend in planetary mixer. Granules were dried in Fluidized Bed Dryer (FBD) at 50°C and passed through 1 mm (BSS 16#). Dried and sifted granules were lubricated with Aerosil 200, Magnesium Stearate and Talc and compressed the blend for preparing

Dissolution was performed as per USP XXIV in 1.0 liter, 0.1 N Hydrochloric acid, 100 RPM, at 37°C using apparatus 1. Release profile was as follows:

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TIME (HOUR)	% DRUG DISSOLVED
1	22.66
2	27.34
4	37.83
8	54.87
12	66.85

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CLAIMS

1. A solid controlled release oral, buoyant unit dose pharmaceutical
5 composition, which comprises of one or more therapeutic agent / drug , a gel forming husk powder obtained from *Lepidium sativum* seeds, one or more cross-linking enhancer, one or more gas generating component and pharmaceutically acceptable excipients.
- 10 2. The composition according to claim 1 wherein the gel forming husk powder obtained from *Lepidium sativum* seeds is present in amounts of between 5 to 60 % of the total weight of dosage form, the cross-linking enhancer is selected from xanthan gum, karaya gum, cellulose ethers like methyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose and their salts,
5 alginates, polyvinyl alcohols and ethyl cellulose or a combination thereof in amounts of from 0.5 to 10% by weight of the dosage form, gas generating component in amounts of from about 5% to 20% by weight of the composition to give a release profile of between 4 to 12 hours.
- 10 3. The composition according to claim 1 wherein the therapeutic agent/ drug is selected from drugs that are absorbed predominantly from the upper parts of gastrointestinal tract.
4. The composition according to claim 1 wherein the total excipients is
15 present in amounts of between 10 to 40 % by weight of the total dosage form.

5. The composition according to claim 1 wherein the cross-linking enhancer is xanthan gum being present in amounts of from 0.5 to 10 % by weight of the dosage form.
- 5 6. The composition according to claim 1 wherein the cross-linking enhancer is hydropropyl methyl cellulose being present in amounts of from 1 to 15% by weight of the dosage form.
7. A method for production of a solid controlled release oral, buoyant unit dose pharmaceutical composition, which comprises blending one or more
10 therapeutic agent/dug, a gel forming husk powder obtained from *Lepidium sativum* seeds, one or more cross-linking enhancer, one or more gas generating component(s) and pharmaceutically acceptable excipients.
- 15 8. A method according to claim 7 wherein the gel forming husk powder obtained from *Lepidium sativum* seeds is added in amounts of from 10 to 80% of the total weight of dosage form, the cross-linking enhancer is selected from xanthan gum, karaya gum, cellulose ethers like methyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose and their salts, alginates, polyvinyl
20 alcohols and ethyl cellulose or a combination thereof in amounts of from 0.5 to 10% by weight of the dosage form, gas generating component(s) in amounts of from about 5% to 20% by weight of the composition to give a release profile between 4 to 12 hours.
- 25 9. A method according to claim 7 wherein the total excipients added is between 10 to 40 % by weight of the total dosage form.

10. A method according to claim 7 wherein the cross-linking enhancer is xanthan gum which is added in amounts of from 0.5 to 10 % by weight of the dosage form.

5 11. A method according to claim 7 wherein the cross-linking enhancer is hydropropyl methyl cellulose which is added in amounts from 1 to 15% by weight of the dosage form.

12. A method according to claim 7 wherein the composition is made in the
10 form of a tablet capsules and pallets.

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AMENDED CLAIMS

[received by the International Bureau on 2 November 2002 (02.11.02);
original claim 1 amended;
remaining claims unchanged (1 page)]

CLAIMS

1. A solid controlled release oral, buoyant unit dose pharmaceutical composition, which comprises of one or more therapeutic agent/ drug, a selective gel forming powder obtained from only the husk of *Lepidium sativum* seeds, one or more cross-linking enhancer, one or more gas generating component and pharmaceutically acceptable excipients.
2. The composition according to claim 1 wherein the gel forming husk powder obtained from *Lepidium sativum* seeds is present in amounts of between 5 to 60 % of the total weight of dosage form, the cross-linking enhancer is selected from xanthan gum, karaya gum, cellulose ethers like methyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose and their salts, alginates, polyvinyl alcohols and ethyl cellulose or a combination thereof in amounts of from 0.5 to 10% by weight of the dosage form, gas generating component in amounts of from about 5% to 20% by weight of the composition to give a release profile of between 4 to 12 hours.
3. The composition according to claim 1 wherein the therapeutic agent/ drug is selected from drugs that are absorbed predominantly from the upper parts of gastrointestinal tract.
4. The composition according to claim 1 wherein the total excipients is present in amounts of between 10 to 40 % by weight of the total dosage form.

STATEMENT UNDER ARTICLE 19 (1)

The subject application relates to the solid controlled release oral unit dosage pharmaceutical composition whereby the controlled release of a drug or therapeutic agent with varied physico-chemical characteristics upon administration to a human being can be achieved.

The composition of the invention is safe, bioacceptable, and biodegradable in the presence of cross linking enhancer which forms porous but cohesive hydrogel which would entrap gas generated due to a gas generating component in the presence of gastric fluid thereby releasing the drug in a controlled manner over a period of time. The present invention makes advantageous use of husk of *Lepidium sativum* seeds along with cross linking enhancer, gas generating component and pharmaceutically acceptable excipients. Considering that there was no prior knowledge in the art that there is husk covering on *Lepidium sativum* seeds, the identification of such husk and its effective use in the controlled release constitute novel and inventive feature of the present invention. Importantly, the selective use of the husk which is rich in mucilage provides for ready swelling more than 15 times its original volume in the presence of water and biological fluids forming desired gel which in combination with the gas generating component achieves special swelling and gellability characteristics. This is further demonstrated by way of illustrative examples.

In particular the use of gas generating component with the mucilage of the husk causes the system to remain buoyant in the stomach for extended hours. The bio-degradable natural fibre from the said husk in presence of cross-linking enhancer form porous but cohesive hydrogel which entraps gas generated due to gas generating component in presence of gastric fluid releasing the drug in a controlled manner over a period time.

Importantly the husk of *Lepidium sativum* used in the invention has the dual character of retarding the release without stopping the release abruptly which is not known in the art.

In order to clearly and sufficiently define the invention the principal claim 1 has been suitably amended to clearly and sufficiently qualify the invention residing in the selective use of gel forming husk powder from *Lepidium sativum* seeds husk .

In particular, in the amended page 30 claim 1 has now been amended to read "A solid controlled release oral, buoyant unit dose pharmaceutical composition, which comprises of one or more therapeutic agent/ drug, a selective gel forming powder obtained from only the husk of *Lepidium sativum* seeds, one or more cross-linking enhancer, one or more gas generating component and pharmaceutically acceptable excipients." Claims 2 to 4 as appearing in page 30 in the original text remain the same as filed.

Amended claims page 30 is submitted herewith which may kindly be taken on record.

We hereby request that the amended claims be also published along with the International Publication of the application.

INTERNATIONAL SEARCH REPORT

International Application No
PC1/IN 02/00096

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/38 A61K9/52 A61K9/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, SCISEARCH, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BAVEJA S K ET AL: "EXAMINATION OF NATURAL GUMS AND MUCILAGES AS SUSTAINING MATERIALS IN TABLET DOSAGE FORMS PART II" INDIAN JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 51, no. 4, 1989, pages 115-118, 123, XP001096214 ISSN: 0250-474X page 115, left-hand column, paragraph 3 abstract	1-12
Y	US 5 096 714 A (KUHRIS ERIC H) 17 March 1992 (1992-03-17) column 9, line 40 - line 49; claims 1-4 -/--	1-12

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *Z* document member of the same patent family

Date of the actual completion of the international search

23 August 2002

Date of mailing of the international search report

04/09/2002

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentkanal 2
Alt - 12801 Munich

Authorized officer

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INTERNATIONAL SEARCH REPORT

ional Application No
PCT/IN 02/00096

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MATHEWS S ET AL: "SOME PHYSICOCHEMICAL CHARACTERISTICS OF LEPIDIUM SATIVUM (HALIV) SEEDS" DIE NAHRUNG, VCH VERLAGSGESELLSCHAFT, WEINHEIM, XX, vol. 1, no. 37, 1993, pages 69-71, XP001086422 ISSN: 0027-769X abstract; figure 1; table 1 ---	1-12
A	US 4 996 058 A (SINNREICH JOEL) 26 February 1991 (1991-02-26) abstract; claims column 3, line 38 - line 63 -----	1-12

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IN 02/00096

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
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**FORMULARIO UNICO DE OPOSICION
2000-12**

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OPOSICION A:

- | | |
|---|---|
| ☒ Patente de Invención | ☐ Marca Colectiva |
| ☐ Patente de Modelo de Utilidad | ☐ Marca de Certificación |
| ☐ Diseño Industrial | ☐ Lema Comercial |
| ☐ Esquema de Trazado para Circuitos Integrados | |
| Marcas de Productos o Servicios | |

2

**SOLICITUD
PUBLICADA**

Número del expediente: 08-007930
Solicitante: PANACEA BIOTEC LIMITED
Apoderado: JUAN PABLO CADENA SARMIENTO
Título de la nueva creación o denominación del signo:
"COMPOSICIÓN FARMACÉUTICAS DE LIBERACIÓN SOSTENIDA Y
PROCESOS DE LAS MISMAS"

Gaceta: 602 de 31-03-2009, Número de Publicación 1509

3

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	Domicilio: Bogotá, D.C.	TP 71168	

4

FUNDAMENTOS DE LA OPOSICION:

Causa: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000).

AL F

5

Comprobante de pago No. 09-44.454 (Oposición) Fecha 16 Jun/09
(Prórroga) Fecha _____

6

Anexos:

- ☒ Comprobante de pago de la tasa
- ☒ Poderes, si fuere el caso
- ☒ Pruebas de los fundamentos de la oposición
- ☒ Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso
- ☒ Copia de la oposición para el traslado al solicitante.

7

NOMBRE: TITO NOE PARRA MURILLO

FIRMA: _____

C.C/No. 79.579.680 T.P. No. 71168